A Woman With Rheumatoid Arthritis, Sjögren’s Syndrome, Leg Ulcer, and Significant Weight Loss

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CASE PRESENTATION

A 46-year-old African American female presented with a 6-month history of swelling involving both hands and knees, with morning stiffness of 3 hours’ duration. She had difficulty extending both elbows and lifting her arms. She reported dryness of her eyes and mouth, but denied any dyspareunia. Despite a normal appetite, she reported a 49-pound weight loss over 6 months, but had no fever or night sweats and was without gastrointestinal symptoms. She had had a nonphotosensitive rash on her face for the past 3 months, but no alopecia or oral ulcers. Six weeks prior to presentation, she developed an enlarging painful ulcer over the right ankle.

Medical History

The patient had previously undergone surgical fusion of a fracture of the right wrist following a fall in 1995. On a single rheumatology outpatient visit in 2001, she was diagnosed with Sjögren’s syndrome, based on xerophthalmia, xerostomia, bilateral parotid swelling, and positive rheumatoid factor (RF; 264 IU/liter) and antinuclear, anti-SSA, and anti-SSB assays. She had no extraglandular features. The following year, she was diagnosed with pernicious anemia and treated with monthly vitamin B12 injections. Four years prior to her current presentation, she had an unexplained syncope episode that was not associated with headaches, visual disturbance, urinary incontinence, chest pain, or dyspnea, and she had no history of seizures. Computerized tomography (CT) and magnetic resonance imaging of the brain, spiral CT of the chest, electrocardiogram, and cardiac catheterization were all negative for potential etiologies.

Social and Family History

She was married, with 2 children via spontaneous vaginal deliveries, and had no family history of any autoimmune disorder. Her symptoms led to her absence from work for 6 months as a budget analyst. She did not smoke or consume alcohol.

Review of Systems

Urticaria developed with shrimp ingestion and iodine exposure. She denied any Raynaud’s phenomenon, chest pain, dyspnea, headache, or changes in urine color or output. She reported no history of thromboses. Her medications were monthly vitamin B12 injections and naproxen 500 mg twice daily for joint pain.

Physical Examination

At her initial outpatient visit, she was emaciated but in no acute distress. Her weight was 155 pounds, her height was 62 inches, and she had a body mass index (BMI) of 28.3 kg/m². Her pulse was 120 beats/minute, blood pressure was 120/84 mm Hg, and her temperature was 98.0°F. There were no carotid bruits, alopecia, oral ulcers, or thyroid enlargement. She had extensive seborrheic eczema involving the nasolabial folds, eyebrows, and ears. There was a 9 × 3–cm tender ulcer over the right lateral malleolus (Figure 1). She had no palpable purpura, varicose veins, or venous stasis. Both parotid glands were enlarged, with the right firm in consistency but nontender. There was a reduced salivary pool, but satisfactory dentition. Multiple mobile, nontender, rubbery cervical and axillary lymph nodes measuring 1–3 cm were present. Her chest revealed few basal fine crackles but was otherwise clear to auscultation and normal to percussion. The heart examination was normal. Her abdomen was soft and nontender with centrally located striae. She had mild splenomegaly, but no other organomegaly. Bowel sounds were normal.

She used a cane for ambulation. Her musculoskeletal examination was significant for synovitis of the proximal interphalangeal (PIP), metacarpophalangeal (MCP), and wrist joints of both hands, with ulnar deviation of the right
MCP joints and radial deviation of the right wrist joint. She had swan-neck deformities of the third and fourth fingers of both hands. There was a nodule over the left elbow, and impingement but no synovitis of the right shoulder. The lower extremities revealed bilateral knee synovitis with cool effusions. The ankles, midfoot, and feet were unremarkable. Her neurologic examination revealed no deficit and urinalysis was unremarkable.

**Laboratory Evaluation**

She had anemia, with elevated inflammatory indices and hypergammaglobulinemia (Table 1). Serum electrophoresis confirmed a polyclonal gammapathy. She had high titers of RF and anti-cyclic citrullinated peptide (anti-CCP) antibodies and positive antinuclear, anti-SSA, and anti-SSB antibodies. The rapid plasma reagin; anti-Sm, RNP, and double-stranded DNA antibodies; and antiphospholipid panel were negative. She was vitamin D deficient (11.6 ng/ml) but euthyroid. Hepatitis B and C and human immunodeficiency viral assays were negative. Radio-graphs of her hands revealed soft tissue swelling of the PIP, MCP, and wrist joints, corresponding deformities of the clinical examination, and erosive disease of the right PIP, MCP, and wrist joints. There was generalized osteopenia.

**CLINICAL COURSE**

She was diagnosed with rheumatoid arthritis (RA) and Sjögren’s syndrome. Sulfasalazine 500 mg was started twice daily for 2 weeks, and then increased to 2 gm daily, along with hydroxychloroquine 200 mg twice a day. Topical bacitracin was prescribed for the leg ulcer and topical glucocorticoids for the seborrheic eczema. Dermatology consultation of the leg ulcer yielded a diagnosis of pyoderma gangrenosum (PG). Biopsy findings of the ulcer reported sparse interface dermatitis, dense lymphoepithelial inflammation, and dermal fibrosis, with deposits of CD3+ cells and sparse CD20 and CD30 cells. There was no cytologic atypia, epidermotropism, or necrosis with plasmacytoid infiltrate. Cultures from the leg ulcer grew *Morganella morganii*, sensitive to ciprofloxacin, and a 2-week course was started. She was referred for a hematology consultation.

Four weeks later, her facial seborrheic eczema and joint pain had improved, and the ulcer was less painful but increased in size. The base was clean, with mild elevation of the edges. Methotrexate was added and titrated to 15 mg each week. In error, the patient took daily instead of weekly methotrexate and developed oral mucositis. The mucositis resolved with discontinuation of methotrexate and folic acid 4 mg daily. She was hesitant to restart methotrexate. A CT/positron emission tomography (PET) scan showed no uptake in perihilar (2.9 × 2.1 cm) lymph nodes and the fibrotic changes in both lower lungs were without hypermetabolic activity. There was bulky hypermetabolic adenopathy throughout the superior mediastinum and left prevascular area with nodes measuring 1–2 cm and a standard uptake value of >6. Lymph nodes in the right paratracheal distribution and the supraclavicular, axillae, jugular, and inguinal areas were involved, with intense uptake in the spleen (13.7 cm). Both upper and lower endoscopies were negative. A bone marrow biopsy sample was negative for any abnormality. A left axillary lymph node biopsy was performed.
Table 1. Laboratory results*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normal value</th>
<th>At presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBCs, × 10^3/µl</td>
<td>4.0–10.5</td>
<td>3.9</td>
</tr>
<tr>
<td>RBCs, × 10^6/µl</td>
<td>3.80–5.10</td>
<td>3.27</td>
</tr>
<tr>
<td>Hemoglobin, gm/dl</td>
<td>11.5–15.0</td>
<td>8.3</td>
</tr>
<tr>
<td>Hematocrit, %</td>
<td>34.0–44.0</td>
<td>26.9</td>
</tr>
<tr>
<td>Platelets, × 10^3/µl</td>
<td>140–415</td>
<td>286</td>
</tr>
<tr>
<td>Serum glucose, mg/dl</td>
<td>65–99</td>
<td>72</td>
</tr>
<tr>
<td>BUN, mg/dl</td>
<td>5–26</td>
<td>12</td>
</tr>
<tr>
<td>Serum creatinine, mg/dl</td>
<td>0.57–1.00</td>
<td>0.71</td>
</tr>
<tr>
<td>Estimated GFR, ml/minute/1.73</td>
<td>&gt;59 &gt;59</td>
<td></td>
</tr>
<tr>
<td>Serum calcium, mg/dl</td>
<td>8.7–10.2</td>
<td>8.6</td>
</tr>
<tr>
<td>Serum total protein, gm/dl</td>
<td>6.0–8.5</td>
<td>9.8</td>
</tr>
<tr>
<td>Serum albumin, gm/dl</td>
<td>3.5–5.5</td>
<td>3</td>
</tr>
<tr>
<td>Total globulin, gm/dl</td>
<td>1.5–4.5</td>
<td>6.8</td>
</tr>
<tr>
<td>Total bilirubin, mg/dl</td>
<td>0.0–1.2</td>
<td>0.2</td>
</tr>
<tr>
<td>Alkaline phosphatase, IU/liter</td>
<td>25–150</td>
<td>63</td>
</tr>
<tr>
<td>AST, IU/liter</td>
<td>0–40</td>
<td>17</td>
</tr>
<tr>
<td>ALT, IU/liter</td>
<td>0–40</td>
<td>7</td>
</tr>
<tr>
<td>TSH, IU/ml</td>
<td>0.450–4.500</td>
<td>0.795</td>
</tr>
<tr>
<td>LDH, IU/liter</td>
<td>100–250</td>
<td>248</td>
</tr>
<tr>
<td>ESR, mm/hour</td>
<td>0–20</td>
<td>&gt;140</td>
</tr>
<tr>
<td>CRP level, mg/dl</td>
<td>0.0–0.5</td>
<td>3.9</td>
</tr>
<tr>
<td>Rheumatoid factor, IU/ml</td>
<td>0–13.9</td>
<td>78.5</td>
</tr>
<tr>
<td>Anti–cyclic citrullinated peptide</td>
<td>0–19</td>
<td>118</td>
</tr>
<tr>
<td>Anti-SSA, anti-SSB</td>
<td>0.0–0.9</td>
<td>28.3</td>
</tr>
</tbody>
</table>

* WBCs = white blood cells; RBCs = red blood cells; BUN = blood urea nitrogen; GFR = glomerular filtration rate; AST = aspartate aminotransferase; ALT = alanine aminotransferase; TSH = thyroid-stimulating hormone; LDH = lactate dehydrogenase; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein.

**CASE SUMMARY**

The patient is a middle-aged African American woman with RA, Sjögren’s syndrome, and accompanying lymphadenopathy, splenomegaly, PG of the leg, and significant weight loss. The differential diagnosis of her additional clinical findings included immune-mediated, infectious, and neoplastic etiologies.

**DIFFERENTIAL DIAGNOSIS**

**Immune-mediated disease.** RA is a common cause of secondary Sjögren’s syndrome (1). In this case, both disease entities satisfy their respective diagnostic criteria. She had bilateral hand synovitis lasting in excess of 6 weeks, with positive RF, nodules, and erosions (2). Using recent American College of Rheumatology (ACR)/European League Against Rheumatism 2010 RA criteria, she scored 8 of 10, surpassing the required 6 points for the diagnosis (3). In the absence of salivary gland tissue or ophthalmologic sicca testing, her sicca symptoms involving both the eyes and mouth, along with positive anti-Ro and anti-La antibodies and bilateral parotid enlargement in the presence of a primary rheumatic disorder, were suggestive of secondary Sjögren’s syndrome (4). Sjögren’s syndrome preceding RA is unusual because RA is usually present for many years before sicca symptoms develop (5,6). However, the presence of lymphadenopathy, splenomegaly, leg ulceration, and profound weight loss are not primary features of either disease.

Felty’s syndrome describes leukopenia, leg ulceration due to associated vasculitis, splenomegaly, and frequent infections that occur in RA patients with poorly controlled longstanding disease (7). Felty’s syndrome is more common in women. Patients with Felty’s syndrome often have high RF, nodules, and erosive disease, as did our patient, but it is rare in African Americans. Significant unintentional weight loss may also occur. However, our patient did not have leukopenia or thrombocytopenia and there was no evidence of small-vessel vasculitis; she had no palpable purpura or neurologic deficit, and the skin ulcer biopsy findings showed normal vessels. She also had no history of prior infections. Large granular lymphocyte (LGL) syndrome is similar to Felty’s syndrome, but one-third lack RF positivity and extraarticular features are less common, although Sjögren’s syndrome may occur (8). The distinction of LGL syndrome from Felty’s syndrome lies in the expansion of lymphocyte populations in the blood and bone marrow and the presence of the LGL cell, features absent in our patient.

Generalized lymphadenopathy, arthritis, and weight loss are components of diagnostic criteria for adult-onset Still’s disease (AOSD) (9). However, our patient had highly positive serologies, an unusual finding in AOSD, and did not have spiking fevers with the typical evanescent, non-pruritic, macular rash. She also did not manifest the typical leukocytosis or transaminitis, which provides evidence against this diagnosis as the etiology of her disease complex.

Mixed connective tissue disease or an overlap syndrome inclusive of RA and Sjögren’s syndrome with the possibility of systemic lupus erythematosus (SLE) could not explain her findings. She had no additional ACR criteria for SLE (10), and despite the positive antinuclear antibodies, had negative anti–double-stranded DNA, anti-Sm, and RNP antibodies. The absence of fever, leukopenia, or tender lymph nodes plus the presence of positive serologies made Kikuchi-Fujimoto disease unlikely (11).

Sarcoidosis is a noncaseating, multisystemic, granulomatous disease. Joint, skin, pulmonary, and lymph node involvement can occur. The concurrence of RA and sarcoidosis is uncommon and few cases have been reported (12). Both entities may cause a positive RF, but in our case, the associated positive anti-CCP lends specificity to RA. Both also may lead to parotid gland enlargement, RA via an associated Sjögren’s syndrome. However, despite the splenomegaly and generalized lymphadenopathy, there was no pulmonary reticular disease, no granulomata in the skin biopsy sample, and normal liver-associated enzymes and angiotensin-converting enzyme levels. There was also erosive joint disease rather than the destructive bone cysts characteristic of osseous sarcoid.

Could this be a typical presentation of an uncommon disease? IgG4 multiorgan lymphoproliferative syndrome (IgG4-MOLPS) describes an expanding spectrum of clinical associations (13). In its current description, patients have marked elevation in IgG4 levels, infiltration of affected organs with IgG4+ plasma cells and fibrosis, lym-
A phoplastic infiltrate, storiform fibrosis, an abundance of eosinophils, and obliterative phlebitis. Clinical features include sclerosing cholangitis, retroperitoneal fibrosis, and autoimmune pancreatitis, but infiltration of the prostate, salivary glands, periorbital glands, lungs, and kidneys has been described. There is clinical overlap of IgG4-MOLPS with Sjögren’s syndrome, Kikuchi-Fujimoto disease, and more recently, Reidel’s thyroiditis. Consideration of the diagnosis is required in cases where atypical features of well-known diseases exist (14). Of significance is the absence of synovitis in IgG4-MOLPS. Our patient had no evidence of widespread fibrosis, had normal pancreatic and thyroid function, and although her immunoglobulin levels were normal, we were unable to obtain IgG4 levels in either serum or tissue in our clinical laboratory.

Infectious etiologies. With the established diagnoses of RA and secondary Sjögren’s syndrome, infectious etiologies were entertained to explain the additional findings. Disseminated tuberculosis was considered (15). A purified protein derivative skin test was negative, and there were no pulmonary infiltrates. Chronic viral infections such as hepatitis B and C may present with significant weight loss, anemia, lymphadenopathy, and splenomegaly, but all relevant viral assays were negative (16). In addition, the human immunodeficiency virus (HIV) may result in bilateral parotid gland swelling as part of the diffuse infiltrative lymphocytosis syndrome, but patients are usually seronegative for Sjögren’s syndrome antibodies and are without arthritis (17). Secondary syphilis can lead to a plethora of findings, with epitrochlear nodes providing the clue, but her rapid plasma reagin test was negative (18). In the absence of prior immunosuppressive therapy, cytomegalovirus and toxoplasmosis were considered unlikely.

Malignancy. The constellation of weight loss, lymphadenopathy, and splenomegaly in a patient with RA raises concern for a malignancy. Her RA seropositivity, small rather than large joint involvement, and erosive disease were inconsistent with the angioimmunoblastic lymphadenopathy syndrome (19). RA patients with longstanding disease are at an 8-fold higher risk of developing B cell lymphoma (20). Her lymph nodes were soft and nontender and the lactate dehydrogenase level was normal, but still, she had significant weight loss. A PET scan reported an enlarged spleen and widespread uptake in lymphoid tissue with increased metabolic activity. Despite this finding, the PET scan was unable to distinguish neoplastic from non-neoplastic etiologies of infiltrative lymphoid disease, including systemic sarcoidosis. Tissue differentiation was therefore sought, and a left axillary lymph node biopsy was performed.

DIAGNOSIS

The lymph node biopsy revealed a diagnosis of multicentric hyaline vascular-type Castleman’s disease. The left axillary lymph node biopsy findings revealed a target-like appearance of regressed germinal centers due to the expanded mantle zone with onion skin changes, vessels penetrating into the regressed terminal centers, and interfollicular plasmacytosis, characteristic of hyaline vascular-type Castleman’s disease. Lymph node architecture, however, was preserved (Figure 2). Immunohistochemical stains were positive for CD3 and CD43 on T lymphocytes in the paracortical region. CD20 was expressed on B cells, primarily located in germinal centers and the mantle zone. No cytogenetic chromosomal abnormality was detected and human herpesvirus 8 (HHV-8) immunostaining was negative. Flow cytometry revealed no lymphoid clonal expansion.

DISCUSSION

Not only is this the first report of RA with PG and Castleman’s disease, but other aspects of this case are also intriguing. Secondary Sjögren’s syndrome is present in only 6–10% of RA patients at onset, is correlated with worse disease activity and outcomes, and is predicted by high RF levels, not anti-CCP (1,21). Salivary gland enlargement,
Our patient had Sjögren’s syndrome for 5 years, but only and when occurring together, there is a 2-fold risk (23). have increased risks for the development of lymphomas, oping RA within a year (22). Both diseases are known to enitis was a frequent finding, with 70% of patients devel-

**Table 2. Clinicopathologic classification and features of pyoderma gangrenosum (PG) and Castleman’s disease (CD)**

<table>
<thead>
<tr>
<th>PG</th>
<th>CD</th>
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<tbody>
<tr>
<td><strong>Clinical variants</strong></td>
<td><strong>Typical findings</strong></td>
</tr>
<tr>
<td>Ulcerative PG</td>
<td>Ulceration, rapidly evolving purulent wound (seen in RA)</td>
</tr>
<tr>
<td>Pustular PG</td>
<td>Discrete pustules, self-limited, associated with IBD</td>
</tr>
<tr>
<td>Bullous PG</td>
<td>Superficial bullae, develop ulcerations (seen in myeloproliferative diseases)</td>
</tr>
<tr>
<td>Vegetative PG</td>
<td>Erosions, superficial ulcers</td>
</tr>
</tbody>
</table>

* RA = rheumatoid arthritis; HHV-8 = human herpesvirus 8; IBD = inflammatory bowel disease; HIV = human immunodeficiency virus.

sicca symptoms, and supportive autoantibodies of Sjögren’s syndrome prior to the onset of RA are uncommon, although in one early synovitis cohort, focal sialadenitis was a frequent finding, with 70% of patients developing RA within a year (22). Both diseases are known to have increased risks for the development of lymphomas, and when occurring together, there is a 2-fold risk (23). Our patient had Sjögren’s syndrome for 5 years, but only developed symptoms of RA 4 years later. Given her presentation with established erosive disease, however, it is likely that subclinical disease existed much earlier. Further, the presence of subcutaneous nodules and high RF and anti-CCP levels and marked elevation in both the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) level all indicate high disease burden and portend a poor outcome. The PET scan reporting widespread lymph node and spleen uptake in conjunction with pronounced right paratracheal lymphadenopathy was highly suggestive of sarcoidosis and would be a third diagnosis in our patient. Sarcoidosis occurring with RA is reportedly rare (10 cases), and similarly, only 6 cases have been reported with Sjögren’s syndrome (12,24). Sarcoidosis has also been reported to develop in RA patients treated with anti-tumor necrosis factor (anti-TNF) biologic therapy, which our patient did not receive (25).

PG is a rare, painful, neutrophilic dermatosis, affecting mostly women ages 20–50 years, and 4 variants are described (26) (Table 2). The lower extremity, mainly pretibial areas, are affected, but other cutaneous and extracutaneous sites (upper airway mucosa, eye, genital, lung, spleen, and muscle), including adjacent sterile cortical osteolysis of the ulnar styloid, are reported (27). The typical lesion is that of a rapidly expanding follicular pustule, with undermined borders and subsequent secondary bacterial infection. PG lesions may be solitary or multiple, and the diagnosis is a clinicopathologic correlation with the underlying condition and exclusion of immune and infectious mimics. In approximately one-half of patients, either inflammatory bowel, hematologic, malignant, or rheumatic disease is found. Up to ~40% of patients with PG have associated arthritis, and both seropositive and seronegative forms, including a large joint, erosive, monarticular variant, have been reported (28). PG patients with arthritis have poor wound healing. Potential contributors include loss of ankle mobility and predisposition to venous stasis, fragile skin from immunosuppressive therapies, arterial disease, and poor nutrition status.

PG in patients with RA is uncommon. The ulcerative type is described and the lower extremities are also the preferred location. Skin lesions often exceed 10 cm in diameter, and extend to involve the muscle, fascia, and tendons (26,29,30). As PG occurs in RA patients with severe longstanding disease, its presence may indicate an increased lymphoma risk. Few reports exist of PG beyond RA, and include Felty’s syndrome and as a paraneoplastic manifestation of myeloproliferative disease (31,32). Fewer reports exist of PG occurring with Castleman’s disease, and none with concurrent RA (33,34). PG treatment is challenging, whether with topical or systemic immunosuppressive therapies, and skin transplants may be required, although local debridement risks development of pathergy. Whereas a response to methotrexate has been documented in RA patients with PG, treatment with anti-TNF therapy has been reported to cause PG, prevent its development, or lead to its resolution (35–37).

Castleman’s disease is a rare nonclonal angiofollicular lymphoproliferative entity with an unknown prevalence, and is classified by the National Cancer Institute as an orphan disease (38). Depending on histology, Castleman’s disease is classified as hyaline vascular or plasmacytic with mixed cellularity (39) (Table 2). The etiopathogenesis is unclear, but the identification of HHV-8 in Castleman’s disease lymph nodes of mainly HIV-positive patients and its viral homology for interleukin-6 (IL-6) have channeled antiviral and biologic-targeted therapies. Excess IL-6 in Castleman’s disease also leads to up-regulation of Th2 cells, B cell growth factors, and vascular endothelial growth factor, resulting in phenotypic expressions as autoimmune phenomena, lymph node enlargement, and vascularity, respectively. Castleman’s disease may present
with asymptomatic single lymph node involvement (unicentric), which is usually of the hyaline vascular type and mostly occurs in patients negative for HIV. Multisite lymph node involvement (multicentric Castleman’s disease) is accompanied by hepatosplenomegaly in as many as 70% of patients and is mostly of the plasma cell type, although at one referral center, 30% were reported to have hyaline vascular histology (38). Symptomatic disease reflects IL-6 expression, i.e., anemia, constitutional symptoms, and elevated CRP and ESR values (Table 3). The clinical course may be self-limited, but most patients are at risk of death from active multicentric Castleman’s disease or progression to non-Hodgkin’s lymphoma (40). Single-site disease is amenable to a course of glucocorticoids, surgical resection, or radiation. Generalized involvement often requires chemotherapy due to either a lack of efficacy or the high risk/benefit ratio of prolonged glucocorticoid administration. Current therapies for multicentric Castleman’s disease indicate a favorable long-term prognosis in patients negative for HIV, and although improved in patients positive for HIV, remains relatively guarded.

Reports of Castleman’s disease in patients with rheumatic diseases are few. Associations of Castleman’s disease with Sjögren’s syndrome and/or RA are anecdotal, and mimickers of the disease are reported as IgG4-MOLPS or AOSD (41–44). Recent studies also underscore the pleiotropic role of IL-6 in RA, where increased levels in synovial fluid indirectly promote osteoclastogenesis by increasing the release of RANKL by osteoblasts and synovial cells (45,46). Randomized controlled trials with monoclonal IL-6 receptor antibodies (tocilizumab) in both RA and Castleman’s disease have demonstrated efficacy, and in Japan, tocilizumab is approved for HIV-negative Castleman’s disease (47–49). However, in Castleman’s disease, the response with tocilizumab is temporary due to the emergence of neutralizing antibodies (50). The immunopathogenic role of CD20-positive B cells in RA and Sjögren’s syndrome is documented, and in Castleman’s disease correlates with a near-complete response of the hyaline vascular type to rituximab (51–53). In RA patients who responded inadequately to TNF, rituximab is an alternate disease-modifying antirheumatic therapy, and in patients with Sjögren’s syndrome, small studies report equivocal efficacy, with improvement in individual disease parameters in the early stages of treatment (54,55).

Our patient had significant weight loss, which can occur in both Sjögren’s syndrome and RA. In the former, xerostomia, loss of taste, poor dentition, and dysphagia are plausible contributors. In RA, cachexia results from excessive proinflammatory cytokine up-regulation (56). Two types of cachexia have recently been described in RA patients: “classic” and “rheumatoid” (57). In the classic type, as seen in cancer, chronic heart failure, chronic kidney disease, or chronic infection, there is loss of both muscle and fat mass, with increased BMI (>25 kg/m²), the result of low muscle mass, but increased fat deposition. There is the suggestion that in defining the metabolic syndrome in RA patients, the BMI component of the syndrome should be greater than 28 kg/m², rather than the customary 30 kg/m² (58). However, the relationship of

| Table 3. Distinguishing features of IgG4 multiorgan lymphoproliferative syndrome (IgG4-MOLPS), sarcoidosis, and Castleman’s disease* |
|---------------|-----------------|------------------|
| Demographics  | IgG4-MOLPS       | Sarcoidosis      | Castleman’s disease |
| Age, years    | Median 69       | Range 10–40      | Median 64           |
| Sex           | M:F 8:1         | F > M            | M:F 2:1             |
| Race/ethnicity|                 | African descent  |                 |
| Constitutional symptoms | Absent | May be present | Present |
| Body cavity effusion | Rare | Uncommon | Common |
| Laboratory data | Polyclonal gammopathy | Polyclonal gammopathy | Polyclonal/multiclonal gammopathy, anemia, ↑ ESR |
| LDH/albumin   | ↑ IgG4 (especially multisite) | High-titer RF | Variable/decreased |
| IL-6 and CRP level | Normal/normal | Normal | Variable/decreased |
| Histopathology | Multiple mass lesions (pancreas, hepatobiliary tract, salivary glands, orbit, lymph nodes) | Systemic disease (lungs, skin, joint, eye) | Unicentric, multicentric lymph nodes, liver, spleen |
| Treatment     | Excellent GC response | Steroid responsive | Unpredictable outcome |
|               | Steroid-sparing agents | may be required | Improved with tocilizumab, rituximab |

* ↑ = increased; ESR = erythrocyte sedimentation rate; RF = rheumatoid factor; ANA = antinuclear antibody; LDH = lactate dehydrogenase; IL-6 = interleukin-6; CRP = C-reactive protein; GC = glucocorticoids.
rheumatoid cachexia to cardiovascular risks and disease outcomes remains unclear, and reversal appears independent of traditional or biologic disease-modifying antirheumatic drug therapy. Despite an almost 50-pound weight loss and the additional diagnosis of a malignancy, our patient maintained a normal range BMI of 28.3 kg/m², but it was a significant decrease from an obese range BMI of 37.3 kg/m² 10 years prior to symptom onset. In determining whether significant weight loss is the result of inflammatory rheumatic disease or malignancy, the relevance of baseline BMI (low, normal, obese) prior to symptoms and/or the actual change in BMI remain unclear. Incorporation of BMI and/or anthropometric measures in RA patients who experience weight loss may provide the necessary data to permit differentiation in causation between primary disease and more sinister causes.

PATIENT'S COURSE FOLLOWING TREATMENT

The patient was treated with rituximab, given at weekly doses of 375 mg/m² for 4 weeks. On a followup rheumatology visit 1 month later, she felt well, had regained 10 lbs, and had a decrease in swelling and firmness of both parotid glands. The leg ulcer had healed (Figure 1). Eight weeks later, although still feeling well, there was an increase in her joint count with early breakdown of the leg ulcer at its inferior margin. She received another cycle of 4 weekly doses of rituximab with complete resolution of the ulcer at its inferior margin. She received another cycle of 4 weeks. On a followup rheumatology visit 1 month later, she felt well, had regained 10 lbs, and had a decrease in swelling and firmness of both parotid glands. The leg ulcer had healed (Figure 1). Eight weeks later, although still feeling well, there was an increase in her joint count with early breakdown of the leg ulcer at its inferior margin. She received another cycle of 4 weekly doses of rituximab with complete resolution of the parotid swelling. She agreed to restart weekly methotrexate. At her last visit almost a year after presentation, she weighed 177 pounds with a Disease Activity Score in 28 joints–CRP score of 1.8, and had returned to full-time employment.

FINAL DIAGNOSIS

Rheumatoid arthritis with Sjögren’s syndrome, pyoderma gangrenosum, and multicentric hyaline vascular-type Castleman’s disease.

ACKNOWLEDGMENT

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Kerr had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Kerr, Aggarwal.

Acquisition of data. Kerr, Aggarwal, McDonald-Pinkett.

Analysis and interpretation of data. Kerr, Aggarwal.

REFERENCES